10. Mammalian cell line CHO dhfr-/pD40458 (Accession NO: KCTC 0632BP) transfected with the expression vector pD0458 of claim 6.

11. A process of preparing a human thrombopoietin derivative comprising culturing a mammalian cell line containing the recombinant gene of claim 3 and obtaining a human thrombopoietin derivative from the cultured mammalian cell line.

12. A pharmaceutical composition containing the human thrombopoietin derivative of claim 1.

REMARKS

I. Introduction

In response to the Office Action dated February 6, 2002, claim 1 has been amended. Claims 1-12 remain in the application. Reconsideration of the application, as amended, is requested.

II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of responding to the Examiner's restriction requirement, and were not required for patentability or to distinguish the claims over the prior art. The amendment is supported by the application as originally filed, e.g., at pages 20-23 and Figure 10, and entry of this amendment is respectfully requested.

III. Examiner Interview Summary

Record is made of a telephone interview held on April 1, 2002, between Applicants' undersigned attorney and Examiner Spector in connection with the present patent application. Applicants gratefully acknowledge the Examiner's helpfulness in clarifying the issues and identifying constructive steps toward a provisional resolution.

The interview centered on discussion of the restriction requirement, the amendment of claim 1 as presented herein, and balancing Applicants' interest in obtaining a single examination of all

claimed subject matter linked by a common inventive concept against the burden on the Examiner to search a number of derivatives. A provisional understanding was reached and Applicants' representative has made a good faith effort to prepare this response in accordance with that understanding. Should the Examiner find further action necessary to compliance with the restriction requirement or placing the application in condition for allowance, the courtesy of a telephone call would be greatly appreciated.

IV. Restriction Requirement

At pages 2-3 of the Office Action, the Examiner required an election of one of 24 identified species of the generic invention claimed. In response, Applicants provisionally elect [Asn^{108}, Asn^{117}, Asn^{164}] hTPO for initial examination, with traverse.

The Examiner alleges that the 24 species, identified as individual N-linked glycosylation sites or combinations of such sites, lack unity of invention because they do not relate to a single general inventive concept under PCT Rule 13.1. Applicants respectfully disagree, and assert that restriction is improper because the subject matter of each of the claimed derivatives is linked by a common inventive concept, the identification of glycosylation sites that provide hTPO derivatives having biological activity equal to or greater than that of native hTPO.

Applicants respectfully disagree with the Examiner's statement in the paragraph bridging pages 2-3 of the Office Action, that the generic concept of artificially glycosylated hTPO does not constitute and advance over the prior art and cannot be the basis for unity of invention. As discussed in the specification, e.g., at page 6, line 6, to page 7, line 13, the introduction of additional sugar chains is not always accompanied by an increase in the catalytic activity of the glycoprotein. TPO Not a catalyst Attempts in the prior art to introduce additional sugar chains into hTPO derivatives resulted in reduced biological activity as compared to native hTPO. Applicants, however, have identified specific glycosylation sites that give rise to hTPO derivatives that have biological activity equal to or greater than that of native hTPO.

Support for this enhanced biological activity is provided in the specification, e.g., at pages 20-23 and Figure 10, in particular. The biological activity of the numerous derivatives prepared by

the inventors was tested both *in vitro* and *in vivo*, by measuring proliferation of megakaryocyte leukemia cells and platelet levels in mice treated with the hTPO derivatives. Data for derivatives showing the highest biological activity are presented in Figure 10.

Applicants note that the claims are not directed to the generic concept of artificially glycosylated hTPO, but rather to derivatives of hTPO that exhibit biological activity that is equal to or greater than that of native hTPO. Claim 1 has been amended to clarify its scope and to limit the recited glycosylation sites to those identified in the specification as preferred (see, e.g., page 7, lines 5-13) on the basis of data demonstrating their enhanced biological activity.

V. Conclusion

Consequently, Applicants respectfully request the Examiner reconsider and withdraw the restriction requirement. It is also submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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KSC/sjm

G&C 118.7-US-WO

APPENDIX: CLAIM IN MARKED-UP FORM

(Due to brackets in original claim, deleted material is enclosed in "{}".)

1. (TWICE AMENDED) A human thrombopoietin derivative which is derived from human thrombopoietin (hTPO) described by SEQ ID NO: 30; which elicits approximately equal or greater biological activity as compared to native hTPO; which has at least one additional N-linked glycosylation site; and which is selected from the group consisting of:

[Asn^{108}] hTPO;

[Asn^{117}] hTPO;

{[Asn^{147}] hTPO;

[Asn^{153}] hTPO;}

[Asn^{164}] hTPO;

[Asn^{193}] hTPO;

{[Asn^{117}, Asn^{147}] hTPO;}

[Asn^{117}, Asn^{164}] hTPO;

{[Asn^{108}, Asn^{147}] hTPO;}

[Asn^{108}, Asn^{164}] hTPO;

{[Asn^{147}, Asn^{164}] hTPO;

[Asn^{117}, Asn^{147}, Asn^{164}] hTPO;

[Asn^{108}, Asn^{147}, Asn^{164}] hTPO;}

[Asn^{108}, Asn^{117}, Asn^{164}] hTPO; and

[Asn^{157}, Asn^{164}] hTPO{;

[Asn^{162}, Ser^{164}] hTPO;

[Asn^{162}, Thr^{164}] hTPO;

[Asn^{153}, Ser^{155}, Asn^{164}] hTPO;

[Asn^{153}, Thr^{155}, Asn^{164}] hTPO;

[Asn^{159}, Ser^{161}, Asn^{164}] hTPO;

[Asn^{159}, Thr^{161}, Asn^{164}] hTPO;

[Asn^{166}, Ser^{168}] hTPO;

[Asn^{166}, Thr^{168}] hTPO; and

[Asn^{164}, Asn^{168}] hTPO}.